I. SEARCH FOR RESTRICTED ROTATION BETWEEN SINGLY LINKED ALIPHATIC CARBON ATOMS

II. PREPARATION OF SOME ANALOGUES OF TETRAHYDROCANNABINOL

BY

HARRY FREY KAUFFMAN, JR.

B.S., University of Virginia, 1941

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1950

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PART ONE

SEARCH FOR RESTRICTION OF ROTATION BETWEEN SINGLY LINKED ALIPHATIC CARBON ATOMS

Introduction

From a number of hindered cinnamic acid derivatives stable isomers have been obtained due to total restriction of rotation about single bonds between one aliphatic and one aromatic carbon atom.[1] Whitehill[2] and Voris[3] had attempted to prepare compounds having highly hindered aliphatic C-C single bonds wherein the aromatic ring of the hindered cinnamic acid residue was replaced by a bulky triarylmethyl or trialkymethyl residue. The present research was an extension of their work.

Three separate lines of experimental attack were followed: (1) an attempt to prepare γ-phenyl-γ,γ-di-*o*-tolyl-α,β-dibromocrotonic acid (I), (2) the preparation of γ-methyl-γ,γ-diethyl-α,β-dibromocrotonic acid (II) and an attempt to isolate rotation isomers of this substance and (3) when these two lines of attack failed, investigation of the condensation reaction between diphenylphenylethynylchloromethane and reactive aromatic compounds as a possible route to compounds of the 3,3,3-triarylpropene-1 type.

Experimental Results

The projected synthesis of γ-phenyl-γ,γ-di-*o*-tolyl-α,β-dibromocrotonic acid (I) appeared to fail at the first step, namely the conversion of 1-phenyl-1,1-di-*o*-tolylpropanone-2 (III), which was available by a procedure of Voris (*loc. cit.*), into 3-phenyl-3,3-di-*o*-tolyl-2-chloropropene. Only oily products were obtained by the action of phosphorus pentachloride on the ketone III either when the reactants were fused near 120° or when they were in solution in pure phosphorus oxychloride.

Voris (*loc. cit.*) had suggested the use of γ-methyl-γ,γ-

diethyl-α,β-dibromocrotonic acid (II) in the study of totally restricted aliphatic C-C single bonds. He had also outlined the method of synthesis used in the present work. The procedure of Davis and Marvel[4] for the preparation of 3-methyl-3-ethylpentyne-1 was repeated. This substance was converted to the corresponding acetylenic acid by successive reaction with ethylmagnesium bromide and carbon dioxide. The acetylenic acid reacted with bromine to give the desired dibromo adduct II.

Two crystalline isomers (presumably *cis-trans* isomers) of II were obtained from the bromination reaction. No success was had in isolating a third isomer (necessarily either a structural isomer or a rotation isomer) from the remaining oily products of this reaction or from various oils resulting from photochemical isomerizations. Because of the liquid nature of these materials the absence of a stable rotation isomer could not be shown.

Resolution attempts with quinine and with *d*-(+)-pseudoephedrine were made on the lower-melting isomer of II. The resolution experiments were complicated by slow decomposition or isomerization of II on standing in solution, particularly in the light, but it was thought that resolution was not being accomplished under the conditions tried. Resolution of the higher-melting isomer of II was not attempted.

Attention was then turned to the development of a new synthetic route to compounds having the 3,3,3-triarylpropene skeleton. As a model reaction possibly useful for subsequent application to more highly hindered systems, the condensation of diphenylphenylethynylchloromethane with phenol, *m*-cresol, resorcinol dimethyl ether, durene, isodurene and 2-methylnaphthalene was studied. The desired products were tetraarylpropynes, which might react with bromine to produce 1,2-dibromo-1,3,3,3-tetraarylpropenes. Some compounds of the latter type have hindered aliphatic C-C single bonds.

From this condensation reaction no substituted tetraphenylpropynes could be obtained in crystalline form. Oily

products having free hydroxyl groups were obtained from phenol and *m*-cresol, but they could not be purified. Crystalline condensation products of structure unknown but different from that of tetraphenylpropynes were obtained with durene and *m*-cresol. Reaction of diphenylphenylethynyl carbinol with resorcinol led to crystalline products which were apparently benzopyran or benzofuran derivatives. Under the same conditions diphenylphenylethynyl carbinol did not condense with phenol or *m*-cresol. Thus it appeared that the condensation reaction between reactive aromatic compounds and diphenylphenylethynylchloromethane or the corresponding carbinol was not promising as a route to hindered 1,3,3,3-tetraphenylpropene derivatives.

Examination of Three-Dimensional Models

In order to search for other types of compounds besides 3,3,3-trialkyl- or triarylpropenes which have hindered aliphatic C-C single bonds and in order to clarify certain theoretical uncertainties, a method was developed for quite approximate prediction of the stability of rotation isomers from three-dimensional scale models.

The method was applied to a number of different types of compounds. Butadiene derivatives appeared geometrically and mechanically to be the type of compound most favorable for demonstrating total restriction of rotation about aliphatic C-C single bonds.

Methods of predicting the kind of isolable rotational forms from the rates of interconversion of the various rotation isomers of a compound were discussed. It was shown that one of the possibilities in certain mechanical situations is to obtain two optically inactive isomers due to total restriction of rotation of one pivot bond.

It was pointed out that compounds of the 3,3,3-triarylpropene type contain highly hindered aromatic-aliphatic C-C single bonds in addition to hindered aliphatic-aliphatic C-C single bonds. Isolation of two rotation isomers of a compound

of this type would consequently not be rigorous proof of total restriction of rotation of an aliphatic C-C single bond.

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PART TWO

PREPARATION OF SOME ANALOGUES OF TETRAHYDROCANNABINOL

Introduction

Various derivatives of tetrahydrocannabinol, when injected into test animals have been shown to have physiological effects similar to those of marihuana. In connection with the study[1] of the change in marihuana potency resulting from change of various structural features of the tetrahydrocannabinol molecule it was desirable to prepare and submit for physiological testing the compounds containing sulfur and nitrogen in partly saturated carbocyclic ring.

Results

The compounds whose syntheses were attempted were 1,2,3,4-tetrahydro-3,5,5-trimethyl-8-*n*-amyl-10-hydroxy-5*H*-pyrido[3,4-*b*]-benzopyran (I) and 1,2-dihydro-5,5-dimethyl-8-*n*-amyl-10-hydroxy-4,5*H*-thiapyrano[3,4-*b*]-benzopyran (II).

The preparation, but not the testing for marihuana potency, of the nitrogen-containing analogue I had been reported by Anker and Cook[2]. Their scheme followed the usual one of Adams and Baker[3]. It involved the condensation of 1-methyl-3-carbethoxy-4-piperidone with olivetol and treatment of the pyrone so obtained with methylmagnesium iodide. Repetition of their procedures produced too little material for testing for marihuana potency. There was some indication that the nitrogen-containing ring may have opened at some time during the condensation reaction or subsequent treatment with methylmagnesium iodide to give a compound of structure different from I.

The synthesis of the sulfur-containing analogue was attempted in similar manner. Olivetol was condensed with 3-carbethoxytetrahydrothiapyrone-4 to give a pyrone. Treatment of this with methylmagnesium halides under a variety of conditions, and subsequent dehydration did not give pure II but resulted in removel of all or part of the sulfur. The crude products could not be purified and an attempt was made to isolate 4-(2,6-dihydroxy-5-*n*-amylphenyl)-3-dimethylhydroxymethyl-5,6-dihydro-1,2-thiapyran, which is presumably the primary product of the Grignard reaction. Some crystalline material which may have been this compound was obtained but it was quite unstable and was available in too small amount to convert to an isolable amount of the corresponding pyran.

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VITA

The author was born July 26, 1920 in Prince Edward County, Virginia. He passed through the public school system in and near Petersburg, Virginia. After four years at the University of Virginia he was graduated with the degree of B. S. in Chemistry in June, 1941. He has pursued graduate study at the University of Illinois since September, 1941 with the exception of the period between June, 1944 and March, 1946, when he served as research chemist at the Central Research Laboratory of Allied Chemical & Dye Company at Morristown, N. J. During his graduate study he held a University scholarship, two University fellowships and was a teaching assistant for five semesters.